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Preface

Mitochondrial dynamics and physiology

Mitochondrial research in the last decade has led to a dramatic expansion of the existing paradigms that define mitochondrial behavior and function. It is now established that mitochondria are highly dynamic, functioning within an interconnected reticulum that fuse, branch and fragment. As the field has evolved, our mechanistic understanding of these processes has become much more refined, however there are still a great deal of unanswered questions into the regulation and meaning of mitochondrial acrobatics. This special issue is dedicated to an examination of recent mechanistic and technical developments in mitochondrial dynamics, and to the contribution of these processes in mitochondrial quality control pathways.

Beginning with new topics in mitochondrial fission, *Mike Ryan* and colleagues explore the complex regulation of the fission GTPase Drp1: from its post-translational modifications to the growing list of adaptor proteins that modulate its recruitment on mitochondria. With an eye towards the physiological importance of these modifications, this review provides a very unique perspective. *Mafalda Escobar-Henriques* and *Fabian Anton* focus their sights on the mechanisms that regulate mitochondrial fusion and tubulation. The importance of proteolytic regulation and ubiquitination in fusion is highlighted, along with a description of the open questions in the field. Within the inner membrane, *Pascale Belengeur* and *Luca Pellegrini* review recent advances in the regulation of cristae dynamics and inner membrane fusion. Exploring the function of the inner membrane GTPase Opa1, they consider the mechanistic basis by which mutations in Opa1 underlie the progression of autosomal dominant optical atrophy. In addition, the authors discuss emerging roles for Opa1 in the regulation of calcium homeostasis and its potential role on lipid droplets.

Another core determinant of mitochondrial morphology and positioning is the regulation of mitochondrial motility upon microtubule tracks. To address new advances in our understanding of how mitochondria move, *Xinnan Wang* takes us through the regulation of both anterograde and retrograde transport, as well as the role of actin as a determinant of mitochondrial position. Focusing in the neuron in health and disease, she examines a number of different model organisms and what we have learned about the interconnectivity between the motility machinery and multiple aspects of mitochondrial function.

A critical element of mitochondrial dynamics is the increasing evidence for the role of proteolytic cascades in the regulation of mitochondrial fusion, lipid transport, and ultimately quality control and cell death. This topic is the focus of an insightful review from the lab of *Thomas Langer*. Starting with the established role of mitochondrial proteases in quality control, they extend their scope to cover the importance of proteases in mitochondrial transcription, translation, phospholipid metabolism, fusion and mitophagy. Continuing in the area of mitochondrial quality control, *Ligia Gomes* and *Luca Scorrano* contributes their voice to discuss the many recent advances in the field of mitophagy. Placing mitophagy in a more global context, they explore the implication of selective vs. non-selective mitophagy and macroautophagy. The functional implications of mitophagy in multiple systems, from yeast to the tissue specific requirements in mammalian cells, are a focus of this review.

The mitochondria are physically and functionally coupled to the endoplasmic reticulum, with the two organelles acting in concert for various functions, from calcium homeostasis to mitochondrial fission and lipid metabolism. The molecular details of this linkage have been an exciting topic of discovery in health and disease, which is covered in a review by *Arun Raturi* and *Thomas Simmen*. Describing recent advances in the field, they also explore the role of oxidoreductases and redox control of mitochondrial to ER contacts, providing new insights into the regulation of contacts.

In addition, this issue also presents new insights into the functional importance of mitochondrial dynamics in heart disease and immunology, presenting some of the first clear roles of mitochondrial dynamics in vivo. *Gerald Dorn* contributes a unique tour of the functions of mitochondrial plasticity in the heart, while *Takumi Koshiba* focuses on the role of mitochondria in immunity. The extreme requirement for ATP makes the heart highly dependent on mitochondrial function and quality control mechanisms. In his review, Gerald Dorn makes a compelling case for why mitochondrial fusion and fission are important to the functioning heart, drawing from the clinic, as well as both fly and mouse models of disease. Mitochondrial dynamics was directly implicated in innate immunity, with the discovery that antiviral signaling complexes form directly on the mitochondrial outer membrane. Takumi Koshiba explores the role of MAVS (mitochondrial anti-viral signaling) in activating the antiviral response, and the contribution of regulatory factors, including the ER and the mitochondrial fusion machinery.

In this issue, we have assembled a series of reviews that bring the reader to the forefront of a rapidly growing area in cell biology. Long known for their metabolic prowess, the mitochondria contribute and respond to cellular cues well beyond respiration and ATP generation. As we uncover the molecular details underlying the core aspects of mitochondrial morphology, we are taken into unexpected areas of physiology. These discoveries continue to advance our field, but more importantly, they provide new directions that expand our conceptualization of a more global cellular role for this fascinating organelle. The future of mitochondrial research is bright, and the contributions made in this issue will provide a touchstone for future work.

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Heidi McBride (Ph.D 1996): Located at the Montreal Neurological Institute at McGill University in Montreal, Heidi has been working in the field of mitochondrial dynamics since obtaining her independent position in 2000. A graduate of McGill with post-doctoral experience at the EMBL-Heidelberg, she currently focuses on the basic mechanisms of mitochondrial vesicle formation, mitochondrial fusion, and the role of mitochondrial SUMOylation in cell signaling pathways. She currently holds a Canada Research Chair, and is a Killam Scholar. She is funded through multiple agencies including the Canadian Institutes of Health Research, the Heart and Stroke Foundation, and the Juvenile Diabetes Foundation. Her website can be found at www.mcbridelab.ca.

Luca Scorrano (MD, 1996, Ph.D. 2000, University of Padova, Italy; postdoc with S.J. Korsmeyer, Harvard Medical School, USA) is a Professor at the University of Geneva (Switzerland). His work contributed to change classical tenets in the field of apoptosis and mitochondrial pathophysiology. He discovered and characterized at the molecular level the process of Opa1-dependent cristae remodeling and identified the first molecular tether between mitochondria and the endoplasmic reticulum. By combining genetics, advanced imaging, cell physiology and electron tomography his lab dissects the role of mitochondrial shape in cell life, differentiation, adaptation and death. He received several national and international Awards for his research and he is EMBO Member since 2012.

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